APPENDIX 1

Structural Abnormalities and Reproductive Failure

Effective Techniques for Diagnosis and Management

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Structural Abnormalities of the Uterus Resulting from DES Exposure

. . . The drug was shown to be beneficial in the treatment of threatened abortion and of . . . abortions that would be anticipated because of previously lost gestations . . .

—O. W. Smith and G. V. S. Smith 1948

. . . The administration of DES . . . did not reduce the incidence of abortion, prematurity or postmaturity.

—W. J. Dieckmann 1953

KEY WORDS: Abortion, Adenosis, Cervical incompetence, Cervical stenosis, Clear cell adenocarcinoma, Diethylstilbestrol (DES), Nonsteroidal estrogens, Prematurity, Stilbestrol, Transplacental carcinogen, T-shaped uterus, Type VII uterine abnormality, Uterine hypoplasia

Although the majority of müllerian anomalies are congenital in nature a unique group of anatomic abnormalities of the male and female

reproductive tracts are secondary to in utero exposure to diethylstilbestrol (DES). The history of DES presents an interesting study in the application of basic science to clinical care and what is known in contemporary parlance as "evidence-based medicine." Interest in nonsteroidal estrogens had been long-standing with efforts focused on developing orally active preparations. Through the 1920s and 1930s active research on sex-hormone biochemistry had been ongoing with particular emphasis on estrogenic substances (1). A variety of estrogenic compounds with varying potency were synthesized through the 1920s and 1930s. In 1933 the compound diethylstilbestrol (DES) was synthesized by E. C. Dodds in Middlesex, London (2). Clinical interest in DES was keen because of its unique effectiveness when administered orally (3,4). Intensive laboratory and clinical studies investigating its potential role in a variety of clinical settings (5) were carried out shortly thereafter. DES was the most widely researched of the synthetic estrogens and found clinical applications in gynecology, endocrinology, and oncology. Due to its powerful estrogenic effect, DES found ready application for the control of vasomotor symptoms, and the early investigations through the late 1930s and early 1940s demonstrated a marked improvement in the relief of the symptoms of menopause in dosages varying from 0.2 to 0.5 mg per day (6). In 1948, an article by Smith and Smith suggested that use of DES prevented recurrent abortion, preterm labor, and preeclampsia (7). The study was largely observational, descriptive, without control groups, and based on the extrapolation of laboratory observations to clinical events. Several similar studies followed, and the drug gained an intense following (8). The efficacy of DES was tested in 1953 by Dieckmann and colleagues in a prospective, double-blind study of 840 women who received the recommended dosage and 806 women to whom placebos were administered (9). The investigators found no benefits among the patients who took DES. The significance of these conclusions was not recognized at the time.

Nevertheless, DES continued to gain popularity. It was used in a variety of expanding clinical circumstances, including menopausal hormone replacement therapy, but had its most profound effect (as revealed by long-term follow-up) when used to prevent first-trimester loss, an effect not related to a reduction in first-trimester abortion but to long-term consequences of its use. So widespread was the use of DES that it was included in a variety of prenatal substances, including prenatal vitamins (Figure 7-1). The drug was used throughout the 1950s and 1960s, and its molecular structure varied somewhat to yield a variety of DES-type drugs (Table 7-1).

Inclusion of DES in a broad array of medications made tracking patients with in utero exposure to DES particularly difficult. The prescribing pattern gained momentum through the late 1950s and early 1960s despite six controlled clinical trials between 1955 and 1965 that failed to demonstrate the efficacy of such therapy. During this time

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Table 7-1. DES-Type Drugs That May Have Been Prescribed to Pregnant Women

Nonsteroidal estrogens		
Benzestrol	Fonatol	Palestrol
Chlorotrianisene	Gynben	Restrol
Comestrol	Gyneben	Stil-Rol
Cyren A	Hexestrol	Stilbal
Cyren B	Hexoestrol	Stilbestrol
Delvinal	H-Bestrol	Stilbestronate
DesPlex	Menocrin	Stilbetin
Dibastil	Meprane	Stilbinol
Diestryl	Mestilbol	Stilboestroform
Dienestrol	Methalienestril	Stilboestrol
Dienoestrol	Microest	Stilboestrol DP
Diethylstilbestrol dipalmitate	Mikarol	Stilestrate
	Mikarol forti	Stilpalmitate
Diethylstilbestrol diphosphate	Milestrol	Stilphostrol
	Monomestrol	Stilronate
Diethylstilbestrol dipropionate	Neo-Oestranol I	Stilrone
	Neo-Oestranol II	Stils
Diethylstilbestrol	Nulabort	Synestrin
Digestil	Oestrogenine	Synestrol
Domestrol	Oestromenin	Synthoestrin
Estilben	Oestromon	Tace
Estrobene	Orestol	Vallestril
Estrobene DP	Pabestrol D	Willestrol
Estrosyn		
Nonsteroidal estrogen-androgen combinations		
Amperone	Metystil	Tylandril
Di-Erone	Teserene	Tylosterone
Estan		
Nonsteroidal estrogen-progesterone combination		
Progravidium		
Vaginal cream suppositories with nonsteroidal estrogens		
AVC cream with dienestrol	Dienestrol cream	

SOURCE: Reproduced by permission from Information for physicians: DES exposure in utero. Washington, DC: US Dept. of Health, Education, and Welfare, 1982. DHEW Publication No. (NIH) 78-1119.

period, an estimated 500,000 to 2 million women in the United States used DES during their pregnancy (10).

When the early studies performed by Smith and Smith in the 1940s were performed, they were state-of-the-art clinical investigations. However, later refinement in experimental techniques and evaluation placed these studies in better perspective. They did not identify and

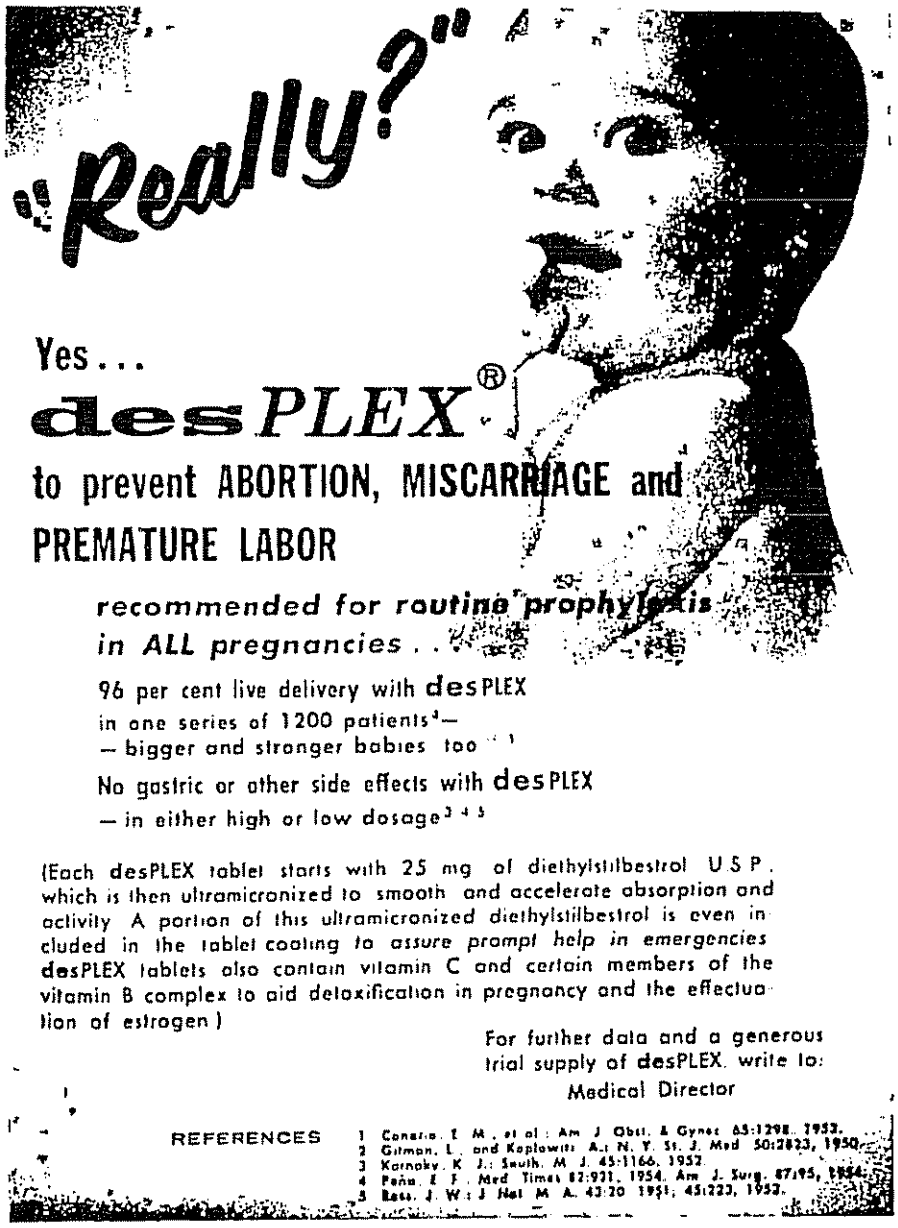

Figure 7-1 Advertisement circa 1955 for desPLEX, a combination of 25 mg DES and vitamins B and C

control confounding variables such as observation bias or recognize the need for randomization or placebo control. The study by Dieckmann was well executed, but its design and conclusions were exceptions to the established trends. At a time when little recognition was given to

study design and quality of clinical data the significance of the strength of the conclusions was lost A recent recalculation of these data revealed that DES significantly increased abortions, neonatal deaths, and premature births (11) A review of early DES literature revealed that all of the DES studies that showed clinical benefit lacked control groups and were not blinded, whereas those reports that failed to show benefit were more carefully designed and had controlled cohorts (12)

However DES usage peaked through the 1960s and physicians continued to prescribe the hormone to many women until 1971 when Herbst reported the association of in utero DES exposure and clear cell adenocarcinoma in young women (13) The association was described in a series of eight cases in which seven patients used DES and none of the mothers of 32 matched controls used the drug The studies by Herbst were carefully executed studies of a case control nature They utilized a retrospective case control method and observed a strong association between DES and subsequent vaginal cancer These studies did not prove cause and effect but clearly demonstrated an association and implicated DES as the etiologic agent The association was confirmed in other studies of young patients with clear cell adenocarcinoma of the vagina or cervix whose mothers described prenatal use of nonsteroidal estrogens, including DES, dienestrol, and hexestrol (14) The influence of DES on the endometrial cavity in particular and the reproductive tract in general was subsequently described (15) These descriptions led to the establishment of an international registry for the study of vaginal adenocarcinoma in patients with a history of in utero exposure to nonsteroidal estrogens The unusual nature of the tumor in young patients contributed to general public alarm and the drug was shortly abandoned for prenatal use

The scope of the risk and size of the exposed population remained unknown for some time further contributing to the panic Studies from the National Cooperative Diethylstilbestrol Adenosis Project (DESAD) soon showed that the risk of adenocarcinoma of the vagina among daughters exposed to DES in utero was lower than some investigators had initially feared (16 17) However, concerns began to grow about the risks for other disease not only among these daughters, but also among the mothers who had taken DES during pregnancy and about sons who had been exposed in utero to DES Concern for anyone exposed to the drug led to the formulation of a unique nomenclature for these groups—DES daughters DES mothers, and DES sons Use of DES was prohibited in the United States in 1971 and in 1973, the Committee on Safety of Medicines in the United Kingdom advised against use of DES during pregnancy (18)

The demographics of this population make DES a relevant topic today Many of those exposed in utero are now 20 to 35 years of age They have reached the reproductive phase of their lives and also the time when they are most at risk for cervical intraepithelial neoplasia

Patients who were exposed to DES will be reaching age 45 in the years ranging from 2000 (for those exposed during 1955, a peak year for prescribing the drug) to 2019 (for those exposed during 1973, the final year for use; 18,19). Whether in utero exposure to stilbestrol has any consequences for women entering menopause and postmenopause will not be known until that time. The changing demographics regarding fertility, that is, age-related changes and patients pursuing fulfillment of their fertility plans at later ages, are important concerns given the data for DES populations. In spite of being a significant point of history, the practical aspect of DES exposure is that these patients will continue to seek medical care for reproductive-related problems well into the next century (19).

Etiology of DES-Related Changes

The effects of in utero exposure to DES are manifested by specific anatomic changes in the upper and lower reproductive tract and induction of benign and malignant changes in the cervix and vagina. The exact manner in which DES exerts these effects on the development of the reproductive tract is unclear. A variety of hypotheses have been put forth for both the malignant and nonmalignant influences on the reproductive tract. However, no clear cause and effect has been demonstrated. Insight as to the possible histogenesis of DES-related abnormalities may be gained from study of the development of the vagina and its squamous character (Figure 7-2).

The anatomic findings in the reproductive tract of DES-exposed patients suggest estrogen-related changes in the columnar epithelium of müllerian origin and the squamous epithelium of the vaginal plate. Though the theory is somewhat debated, the vagina arises from columnar epithelium of müllerian duct origin and a solid core of squamous epithelium or vaginal plate. The plate extends from the urogenital sinus cephalad and eventually becomes canalized to form the permanent lining of the vagina. The process of migration and canalization occurs between the sixth and twentieth week of gestation. The müllerian origin contributes to the strict squamous nature of the vagina and, except in rare cases of Gartner's duct remnants, glandular tissue is not present in the vagina. With the upward growth of the vaginal plate and subsequent canalization, the entire lining of the vagina is characterized by the squamous epithelium of this structure.

The columnar epithelium of müllerian origin persists in a region cephalad to the vaginal plate in the region of the endocervix, endometrium, and fallopian tube. Thus, the dual tissue origin of the vagina, that is, columnar and squamous epithelium, is characterized by a distinct segregation of the columnar epithelium at a region above

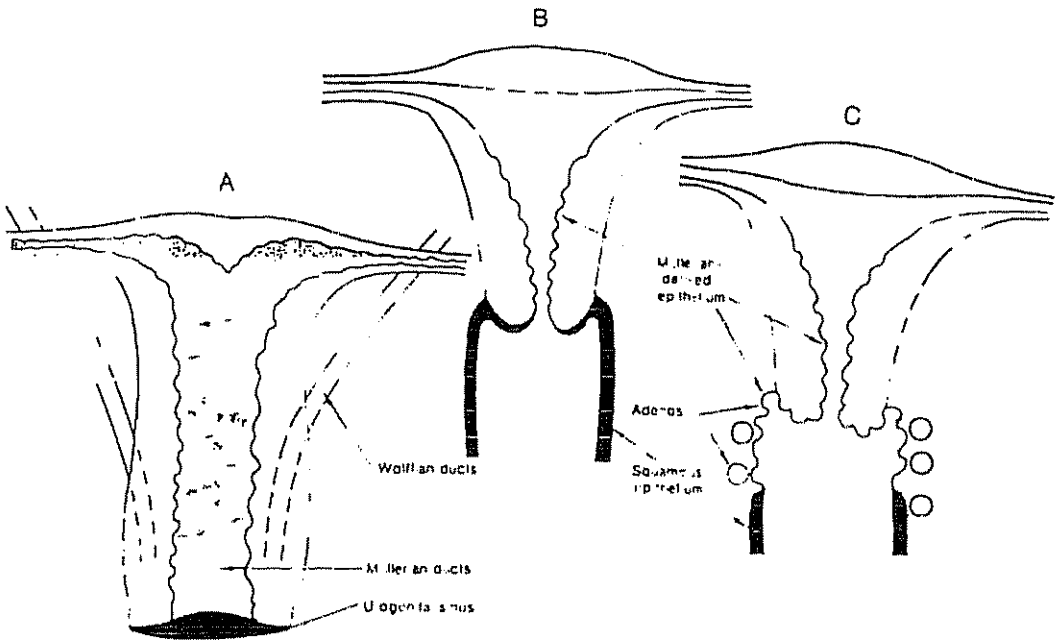

Figure 7-2 Schematic representation of the embryologic development of the vagina in the unexposed and DES exposed woman. Cephalad progression of urogenital sinus derived squamous epithelium (solid black) over mullerian duct-derived columnar mucosa (stippled) early in gestation (A). The wolffian ducts are regressing without testosterone stimulation. Vaginal canal lined by squamous epithelium up to the endocervical canal as found in late gestation in normal female fetuses (B). DES exposure before the nineteenth week of gestation, often causing retention of the mullerian mucosa over parts of the cervix and vagina (adenosis) by interference with the normal migration of squamous epithelium (C), which may also lead to structural changes in the vagina, cervix, uterus, or all these organs. (Reproduced by permission from Stillman RJ. In utero exposure to DES: adverse effects on reproductive tract and reproductive performance in male and female offspring. Am J Obstet Gynecol 1982; 142:905–917.)

the external os of the cervix and with the squamous epithelium below that level. Changes associated with DES exposure appear to be related to a persistence of columnar epithelium in regions typically characterized by squamous cells only (20).

The changes may result from a disturbance of the müllerian epithelium, the vaginal plate, or both and result in the persistence of columnar cells similar to those of the endocervix, endometrium, and fallopian tube at a level below their normal termination in the vicinity of the external os of the cervix. In experimental animals, Forsberg produced a vaginal adenosis-type lesion by administering estradiol to neonatal mice, which suggests a definitive influence related to administration of estrogen (21–23). Further evidence to support the notion that vaginal adenosis may be related to estrogen stimulation is given by the demonstration of estrogen receptors in the mouse fetus and the persistence postnatally of DES influence on the reproductive tract. Abnormal tissue

morphogenesis and neoplasia may also be related to the expression of estrogen-related genes (24) By use of in situ and northern RNA hybridization as well as immunoblotting and immunohistochemistry for lactoferrin and epidermal growth factor (EGF) both subject to steroid regulation, exposure to DES results in the induction of mRNA and proteins encoded by these two genes in the mouse uterus and vagina (25) This induction may be related to the establishment of estrogen effects throughout the reproductive tract, which may be instrumental in the observed changes

Similar changes were noted in mammary glands of rats exposed to DES in utero which supports the premise of transplacental influence of DES on any estrogen sensitive tissues (26) These studies suggested that a marked transplacental estrogen influence by DES is seen at critical areas in the reproductive tract and that these influences may prevent the transformation of columnar epithelium to a stratified form as the vaginal plate grows upward The frequent vaginal and cervical ridges that may be produced by abnormal proliferation of connective tissue of the junction of the müllerian urogenital sinus anlage as well as by structural abnormalities of the endometrial cavity offer additional evidence of an abnormal genital tract development in DES-exposed patients (27)

CLINICAL CORRELATES

Clinically significant changes in the reproductive tract include the development of clear cell adenocarcinoma of the cervix and vagina, nonmalignant conditions and associated changes in the lower reproductive tract and changes in fertility and associated changes in the upper reproductive tract

Clear Cell Adenocarcinoma

The most dramatic DES-related changes described in the literature are those relating to the development of clear cell adenocarcinoma Several cases of clear cell adenocarcinoma of the vagina in adolescent girls in the Boston area of the United States were reported by Herbst and Scully in 1970 (28) This series followed closely a report in the pediatric literature of an unusual clustering of clear cell adenocarcinoma of the vagina in adolescents No association with DES was drawn (29) One year later, a retrospective study linked these cancers with the maternal ingestion of DES during pregnancy (13)

Due to the devastating nature of the disease, public concern grew rapidly as the reports increased The peak epidemic in the United States

occurred in 1975, when a total of 33 cases of clear cell adenocarcinoma was reported. A considerable interest developed among the patients themselves, who formed a variety of interest groups including the DES Action Group UK, DES Action Netherlands, and Women's Health. In part because of the publicity campaigns organized by these interest groups, estimates on women exposed to DES in utero have been continually updated. It has been estimated that during the period between 1940 and 1975 between 189,000 and 378,000 pregnant Dutch women used DES (30). Approximately 375 cases of DES-associated clear cell adenocarcinoma of the vagina and cervix have been reported (31).

The risk of developing clear cell adenocarcinoma, calculated from birth to the age of 34, is estimated to be about 1 for every 1000 women exposed in utero (32). Why clear cell adenocarcinoma develops in only a small proportion of the exposed population is unknown. Herbst reported the findings of a second case-controlled study of the risk factors associated with the development of clear cell adenocarcinoma in DES-exposed women. This study examined 158 cases of the disease in patients with clearly documented DES-exposure from the DESAD Project and 1848 cases obtained from the National Cooperative DES Adenosis Project of DES-exposed women of a similar age without cancer. In this study, the important factors associated with the development of carcinoma included the time of initiation of DES during exposure, a maternal history of early miscarriage, and an autumnal or premature birth.

The most important criteria for the development of clear cell carcinoma may be associated with the period of exposure, dosage, and duration. Herbst reported that women whose mothers were given DES within 12 weeks of pregnancy had a relative risk of developing clear cell adenocarcinoma of the vagina that was triple that for women whose mothers were given the drug during week 13 of gestation or later (33). The youngest patient was 7 years old and the oldest 42 when the tumor was first diagnosed. The number of cases increased substantially in patients after age 14 with a peak between ages 17 to 21 years. Isolated prepubertal cases have been described. One unique case of monozygotic twins has been reported, one of whom developed clear cell adenocarcinoma (34,35). The reported cumulative dosage of the drug varied from less than 200 mg to more than 1800 mg. Although the dose-response relationship has not been clearly established, the critical period of exposure appears to be before the eighteenth week of pregnancy. The major impact appears to occur during the period of 15 to 60 days after conception (an interval of active organogenesis). Thus exposure during this critical period could give rise to both the teratogenic and oncogenic manifestations noted in these patients. As discussed earlier, vaginal adenosis may be induced by steroidal or nonsteroidal estrogens. However, beyond this, the exact teratogenic and carcinogenic effects of transplacental exposure to DES are unknown.

Table 7-2. Changes in Female Reproductive Anatomy

Lower tract changes
Vagina—adenosis
Adenocarcinoma
1:4,1000 women
Exposure in utero before 18 wk
Ages—7–33 yr; peak at 18 yr
Cervix—cervical collar, cockscomb
Upper tract changes
Uterus
T-shaped cavity
Constriction rings
Hypoplasia
Intrauterine synechiae
Fallopian tubes
Abnormal fimbriae
Cornual budding

Lower Tract Changes

Many non-neoplastic abnormalities are found in the lower genital tract of DES daughters (Table 7-2). These malformations include vaginal adenosis and adenocarcinoma, and a variety of anatomic deformities including cervical collars and hoods, cockscomb cervix, and pseudopolyps of the cervix (36,37). Non-neoplastic abnormalities are also present in a small percentage of non–DES-exposed patients (38) and may represent one extreme of a normal distribution. However, the frequency of these abnormalities is increased in DES-exposed populations.

Symptomatic vaginal adenosis has been described in patients without a known history of DES exposure (39). Several nonmalignant processes such as ectropion appear to occur with higher frequency in DES-exposed patients. There appears to be no increased incidence in dysplasia when exposed and unexposed groups are studied from participants in the DESAD project (40,41).

Vagina

The effects in the vagina include adenosis, defined as the presence of mucinous columnar glands characteristic of those in the endocervix located in the upper vagina (10). No untoward effect of adenosis on reproductive function has been described.

Cervix

Several abnormalities in cervical anatomy have been described, including a cockscomb appearance (Figure 7-3), a collar hood appearance, or

Figure 7-3 Cockscomb cervix in a patient with known in utero exposure to DES

a pseudopolyp (10,37). DES-exposed patients with transverse cervicovaginal ridges may be more likely to experience repeated first-trimester loss (42,43). Cervical hypoplasia has also been described and may be diagnosed by ultrasound assessment of the cervical length (44). Other cervical changes have been observed after commonly employed treatments. Using cryotherapy to treat a variety of cervical abnormalities has resulted in stenosis and has placed these patients at risk for anatomic changes that potentially could compromise reproduction (45). Cervical

incompetence at times requiring cerclage placement has also been described (46,47)

Upper Tract Changes

Uterus

The uterus manifests the most dramatic nonmalignant abnormalities of DES exposure (48,49) Numerous benign uterine anomalies of sufficient intensity to potentially affect reproduction have been described including irregularities of the shape of the endometrial cavity T-shaped uterus (Figure 7-4) and hypoplastic uteri Those

Figure 7-4 Hysterosalpingogram demonstrating a hypoplastic uterine cavity characteristically T-shaped consistent with in utero exposure to DES

women who have cervical and vaginal structural abnormalities and vaginal epithelial changes appear to be at greater risk for uterine abnormalities (50)

In a study as part of the DESAD project, among 367 cases found by record review, multivariant analysis indicated a close association of the anomalies in the reproductive tract with the gestational week of first exposure and the total dose The prevalence of the anomalies appeared to be lower among subjects who had been pregnant and higher among those with older age at menarche (51)

Infertility among DES-exposed women is a controversial and much-debated issue. There are several comparative studies suggesting infertility among DES-exposed women It has become common to associate in utero DES exposure with infertility, but the results of these studies are conflicting and inconclusive Early reports also suggested that spontaneous abortion and ectopic pregnancy are increased in exposed women, but comparative well-designed studies subsequently supported this conclusion (52,53) In a study by Muasher fertility rates

Figure 7-5 Hysterosalpingogram showing constricted cavity and peritubular budding

associated with IVF between exposed and nonexposed women were found to be similar, but exposed women appeared to experience obstetrically related problems more commonly than unexposed women (54).

A number of case-controlled studies have evaluated fertility in DES daughters and have found no differences in fertility between exposed and unexposed daughters. However, one study found DES daughters to be less fertile than women who were not exposed in utero (55). In the study by Senekjian that evaluated the causes of primary infertility in daughters exposed and not exposed to DES, it was found that 82% of DES-exposed women conceived and 92% of unexposed women conceived. Adverse outcomes of pregnancy including preterm birth, ectopic pregnancies, and intrauterine deaths have been reported more commonly among DES-exposed daughters than among controls. Unfavorable or adverse pregnancy outcomes were also more common among women who had cervicovaginal ridges on pelvic examination. Despite this, more than 80% of DES daughters who desire pregnancy or who have become pregnant have delivered at least one live-born infant. Approximately 70% of patients have significant changes on hys-

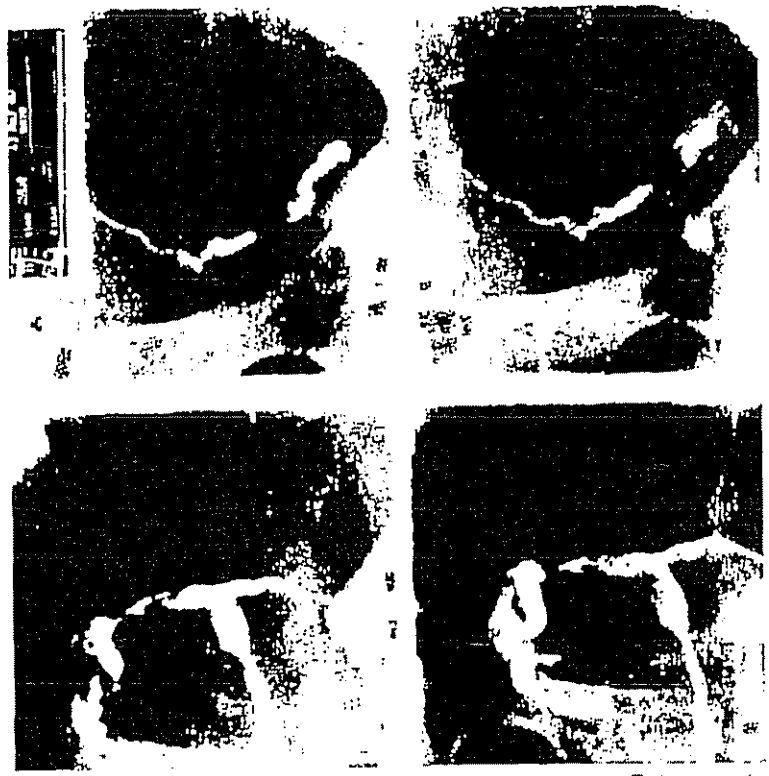

Figure 7-6 Hysterosalpingogram demonstrating characteristic T shape with multiple filling defects (lower panels).

terosalpingography (HSG). In addition to the hypoplastic cervix, cornual budding, peritubular cuffing, and constriction rings have also been described. When assessed for capacity, the internal cavity of the T-shaped uterus has been noted to be smaller than that of controls (Figures 7-5 and 7-6). The histology of the endometrium is usually normal; however, there are marked differences in the stromal integrin expression in patients with in utero exposure to DES, suggesting another etiology to compromised reproduction. In studies that examined the renal system with intravenous pyelography, 25% of patients with in utero exposure to DES revealed renal and ureteral abnormalities (50).

DIAGNOSIS

History of Exposure to DES

The patient's history is the most significant aspect for a patient with exposure to DES. Such a history should lead to increased monitoring for the detection of clinical abnormalities.

Clinical Examination

Meticulous examination of the vagina and cervix should be carried out in all patients with a history of DES exposure. Careful digital examination and palpation of the vaginal walls should also be carried out, and the clinician should hold a low threshold for biopsy of any suspicious lesions. Careful visual inspection of anterior, posterior, and lateral walls of the vagina should be taken with appropriate cytologic sampling. Colposcopic identification of vascular patterns and careful description of the transformation zone is essential. A speculum examination may reveal cervical collar, cockscomb abnormalities, and cervical stenosis. HSG reveals uterine and tubal abnormalities (6,7,56). These abnormalities include a constricted uterine cavity, peritubular cuffing, the cavity itself is frequently hypoplastic and, in its extreme form, T-shaped (see Figures 7-3 through 7-5). In addition, intravenous pyelography performed as part of the evaluation may reveal renal and ureteral abnormalities.

Ultrasonography

The T-shaped uterine cavity may be detected on transabdominal ultrasound by a lack of fundal concavity and narrow fundus (57). On the